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The influence of system delay on 30-day and on long-term mortality in patients with anterior versus non-anterior ST-segment elevation myocardial infarction: a cohort study

Sonja Postma,[1] Jan-Henk E Dambrink,[2] A T Marcel Gosselink,[2] Jan Paul Ottervanger,[2] Evelien Kolkman,[1] Jurrien M ten Berg,[3] Harry Suryapranata,[4] Arnoud W J van 't Hof[2]

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For numbered affiliations see end of article.

Correspondence to
Dr A W J van 't Hof;
v.r.c.derks@isala.nl

ABSTRACT

Aim: To evaluate the relationship between system delay and 30-day and long-term mortality in patients with anterior versus non-anterior ST-elevation myocardial infarction (STEMI).

Methods: We conducted a prospective observational cohort study. Patients with STEMI who were transported to the Isala Hospital, Zwolle, and underwent primary percutaneous coronary intervention (pPCI) from 2005 until 2010 were included. These patients were divided into quartiles of system delay (time from first medical contact until reperfusion therapy): Q1–Q4.

Results: In total, 3041 patients were included in our study. 41% (n=1253) of the patients had an anterior myocardial infarction (MI) and 59% of the patients (n=1788) had a non-anterior MI. Only in patients with an anterior MI, prolonged system delay was associated with a higher mortality (30-day Q1: 2.6%, Q2: 3.1%, Q3: 6.8%, Q4: 7.4%, p=0.001; long-term Q1: 12.8%, Q2: 13.7%, Q3: 24.1%, Q4: 22.6%, p<0.001). After multivariable adjustment, prolonged system delay was associated with a higher 30-day and long-term mortality in patients with an anterior MI (30 day Q2: HR 1.18, 95% CI (0.46 to 3.00), Q3: HR 2.45, 95% CI (1.07 to 5.63), Q4: HR 2.25, 95% CI (0.97 to 5.25)); long-term Q2: HR 1.09, 95% CI (0.71 to 1.68), Q3: HR 1.68, 95% CI (1.13 to 2.49), Q4: HR 1.55, 95% CI (1.03 to 2.33)), but not in patients with a non-anterior MI.

Conclusions: Prolonged system delay significantly increased short-term as well as long-term mortality in patients with an anterior MI. This effect was not demonstrated in patients with a non-anterior MI. Therefore, it is of the greatest importance to minimise system delay in patients who present with an anterior MI.

KEY MESSAGES

What is already known about this subject?
It is known that system delay is independently associated with mortality.

What does this study add?
We hypothesised that the effect of system delay on mortality would be most apparent in high-risk patients (patients with an anterior myocardial infarction) compared with low-risk patients (patients with a non-anterior myocardial infarction).

How might this impact on clinical practice?
Focusing on system delay, especially in high-risk patients, may improve clinical practice since we have demonstrated that prolonged system delay significantly increased short-term as well as long-term mortality in high-risk patients. This effect was not demonstrated in low-risk patients.

INTRODUCTION

As stated in the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) and of the European Society of Cardiology (ESC), it is crucial to perform rapid reperfusion therapy in patients with ST-segment elevated myocardial infarction (STEMI),[1] [2] because every minute of delay in these patients affects mortality.[3] Therefore, currently time delays like system delay, patient delay, transportation delay, door-in-door-out time and door-to-balloon (D2B) time care are of great concern for patients with STEMI.[4–8] System delay, defined as time from first medical contact (FMC, ie, EMS call) to reperfusion therapy, is a relatively new time delay which can be optimised by optimising the system. As demonstrated by Terkelsen et al,[4] system delay was independently associated with mortality. Since we hypothesised that this effect would be the most apparent in high-risk patients, we have investigated the effect of system delay on 30-day and

on long-term mortality in patients with an anterior myocardial infarction (MI) versus a non-anterior MI.

METHODS AND ANALYSIS

Population

All patients with consecutive STEMI, who were transported to our percutaneous coronary intervention (PCI) centre with the intention to perform primary PCI (pPCI), from 2005 until 2010, were prospectively registered in a dedicated database. Criteria for the diagnosis of STEMI were: (1) history of cardiac symptoms for at least 30 min in the last 12 h or between 12 and 24 h if they had persistent symptoms with evidence of ongoing ischaemia; (2) elevated levels of creatine kinase or creatine kinase-MB and (3) concurrent ECG changes: ST-segment elevation of >0.1 mV in at least two adjacent ECG leads.[9]

Infarct size was calculated as the peak level of creatine kinase (peak CK) within 24 h after admission.[10] The municipal registration in the Netherlands was consulted for the mortality of all patients in this study.

The included population was divided into four groups according to the quartiles of system delay (Q1, Q2, Q3 and Q4). System delay was defined as the time from FMC, that is, EMS call to reperfusion therapy. Four other time intervals were also evaluated: (1) symptom onset (SO) diagnosis: time from SO to indication MI (time diagnostic ECG) either in the ambulance or at a spoke centre, (2) diagnosis door PCI: time from diagnosis to arrival at the PCI centre, (3) D2B: time from arrival at the PCI centre to balloon inflation (BI), and (4) total ischaemic time: time from SO to BI.

Patients were excluded if one of the following criteria was met: patients were walk-ins, they were not treated by PCI, D2B time was >180 min, system delay was unknown or mortality could not be retrieved.

pPCI procedure

The staff of the catheterisation laboratory of the PCI centre was preinformed about the estimated time of arrival of the patient and was activated well before the arrival of the patient. In case the staff lived more than 30 min away from the PCI centre, they had to stay in the PCI centre while being on-call. All patients were treated prehospital with an intravenous bolus of 5000 IU of unfractionated heparin and 500 mg aspirin intravenously. During the study period, the administration of clopidogrel on top of aspirin and heparin as prehospital treatment was implemented at 1 July 2006. The administration of GPIIBIIIA blockers in the prehospital phase was left to the discretion of the referring physicians.

The location of the acute vessel occlusion was determined in this study by the PCI operator. Consequently, two groups were made according to the location: left anterior descending artery (LAD; anterior MI) versus non-LAD (non-anterior MI).

Statistical analysis

Statistical analysis was performed with SPSS V.20.0. Continuous data were expressed as mean±SD or median and IQR. Categorical data were presented as percentages. A Kruskal-Wallis test was used for continuous data since these were non-Gaussian distributed. A Pearson's χ^2 test was used for categorical data. The continuous variable infarct size was converted into a dichotomous variable by dividing the de-continuous variable in IQRs and defining the IQR 0.75–1.00 as large enzymatic infarct size (75th centile). A p for trend was calculated for large enzymatic infarct size, and for 30-day and long-term mortality between the quartiles of system delay.

To assess whether anterior MI might interfere with the relationship between system delay and 30-day and long-term mortality, interaction testing was performed.

Logistic regression analyses were performed to estimate the effect of system delay on large enzymatic infarct size. Variables included in the models were age, gender, smoking, diabetes mellitus (DM), hypertension, hypercholesterolaemia, previous MI, previous PCI, previous coronary artery bypass grafting (CABG), type of triage, ST deviation on diagnostic ECG and the quartiles of system delay. Cox regression analysis was performed to estimate the effect of system delay on 30-day and on long-term mortality. Variables included in the models for 30-day mortality were age, gender, DM, hypertension, type of triage, thrombolysis in myocardial infarction (TIMI) risk score and the quartiles of system delay. For the Cox regression analysis of long-term mortality the previous MI, previous PCI and previous CABG were added.

All the above described statistical tests were performed two sided. In all the statistical analyses, p values <0.05 were considered as statistically significant.

The study was conducted according to the principles of the Declaration of Helsinki and the protocol was approved by the local institutional review board. No extramural funding was used to support this work. The authors are fully responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

From 2005 until 2010, 4655 patients were referred to our hospital with the intention to perform pPCI. In total, 312 patients (7.7%) were walk-ins at the PCI centre; 668 patients did not undergo PCI (14.3%); for 344 patients, the D2B time was >180 min (7.4%); for 245 patients, system delay was unknown (5.3%); and in the case of 45 patients (1.0%), mortality could not be retrieved. Of the remaining 3041 patients, 41% (n=1253) of the patients had an anterior MI and 59% (n=1788) had a non-anterior MI. There was a significant interaction effect between anterior infarction and the quartiles of system delay on 30-day (p=0.048) and on long-term mortality (p=0.027). Therefore, the results are presented separately for patients with an anterior MI and patients with a non-anterior MI.

Anterior MI

The baseline characteristics are described in table 1. Patients with a prolonged system delay were older, were less often triaged in the field and had less ST-deviation on the diagnostic ECG. Gender, DM and the TIMI risk score differed among the quartiles of system delay. The time intervals are illustrated in figure 1A. All time delays were significantly different between the quartiles of system delay. The median follow-up time was 5.3 (3.6–6.6) years. System delay was independently associated with a large enzymatic infarct size (Q2: OR 1.85, 95% CI (1.19 to 2.86), Q3: OR 1.80, 95% CI (1.15 to 2.81), Q4: OR 1.15, 95% CI (0.72 to 1.84)). After Cox regression analysis, prolonged system delay was independently associated with 30-day mortality (Q2: HR 1.18, 95% CI (0.46 to 3.00), Q3: HR 2.45, 95% CI (1.07 to 5.63), Q4: HR 2.25, 95% CI (0.97 to 5.25)) and with long-term mortality (Q2: HR 1.09, 95% CI (0.71 to 1.68), Q3: HR 1.68, 95% CI (1.13 to 2.49), Q4: HR 1.55, 95% CI (1.03 to 2.33)) (figure 2A).

Table 1 Baseline characteristics

System delay in quartiles (min)	Q1: 72.0 (62.0–78.0)	Q2: 92.0 (87.0–97.0)	Q3: 114.0 (108.0–121.0)	Q4: 160.0 (142.0–190.0)	p Value
Characteristic					
Anterior MI	(n=313)	(n=321)	(n=323)	(n=296)	
Age years (mean±SD)	62.6±12.5 (n=313)	62.2±12.7 (n=321)	65.8±12.6 (n=323)	64.5±13.2 (n=296)	0.001
Male gender	247/313 (78.9%)	241/321 (75.1%)	218/323 (67.5%)	218/296 (73.6%)	0.011
Previous MI	20/312 (6.4%)	27/321 (8.4%)	34/323 (10.5%)	32/296 (10.8%)	0.189
Previous CABG	3/313 (1.0%)	4/321 (1.2%)	6/323 (1.9%)	3/296 (1.0%)	0.734
Previous PCI	22/313 (7.0%)	24/321 (7.5%)	23/321 (7.2%)	32/296 (10.8%)	0.266
Hypertension	107/313 (34.2%)	88/320 (27.5%)	112/320 (35.0%)	108/295 (36.6%)	0.077
DM	25/313 (8.0%)	31/321 (9.7%)	50/323 (15.5%)	28/296 (9.5%)	0.012
Hypercholesterolemia	50/311 (16.1%)	53/319 (16.6%)	62/321 (19.3%)	67/294 (22.8%)	0.130
Smoking	124/312 (39.7%)	134/319 (42.0%)	111/317 (35.0%)	116/295 (39.3%)	0.332
Killip class >1	292/313 (93.3%)	299/321 (93.1%)	300/323 (92.9%)	265/294 (90.1%)	0.413
TIMI risk score	3.24±2.12	3.22±2.07	3.56±2.09	3.82±2.30	<0.001
(mean±SD, median (IQR))	3.0 (1.0–4.0) (n=311)	3.0 (1.0–5.0) (n=321)	2.0 (3.0–5.0) (n=323)	4.0 (2.0–5.0) (n=294)	
Field triage	269/313 (85.9%)	239/321 (74.5%)	196/323 (60.7%)	134/296 (45.3%)	<0.001
GPIIBIIIA blocker*	82/263 (31.2%)	92/275 (33.5%)	99/283 (35.0%)	99/249 (39.8%)	0.217
ST-segment deviation	13.48±8.76	12.51±7.87	12.51±8.41	11.45±10.53	0.001
(diagnostic ECG)	11.0 (8.0–17.0) (n=201)	11.0 (7.0–16.0) (n=216)	11.0 (7.0–16.0) (n=227)	8.0 (5.0–15.0) (n=220)	
Multivessel disease	130/313 (41.5%)	142/320 (44.4%)	137/322 (42.5%)	119/295 (40.3%)	0.774
Non-anterior MI	(n=462)	(n=429)	(n=448)	(n=449)	
Age years (mean±SD)	62.5±11.7 (n=462)	63.5±12.2 (n=429)	63.1±12.0 (n=448)	63.4±12.1 (n=449)	0.488
Male gender	338/462 (73.2%)	323/429 (75.3%)	318/448 (71.0%)	327/449 (72.8%)	0.556
Previous MI	42/459 (9.2%)	41/427 (9.6%)	37/445 (8.3%)	64/448 (14.3%)	0.015
Previous CABG	10/461 (2.2%)	14/428 (3.3%)	16/447 (3.6%)	28/449 (6.2%)	0.012
Previous PCI	44/461 (9.5%)	44/428 (10.3%)	41/447 (9.2%)	52/447 (11.6%)	0.628
Hypertension	153/460 (33.3%)	137/427 (32.1%)	169/445 (38.0%)	176/446 (39.5%)	0.061
DM	52/461 (11.3%)	41/428 (9.6%)	53/444 (11.9%)	53/448 (11.8%)	0.669
Hypercholesterolemia	122/460 (26.5%)	84/425 (19.8%)	100/444 (22.5%)	111/446 (24.9%)	0.096
Smoking	208/455 (45.7%)	184/426 (43.2%)	210/440 (47.7%)	194/442 (43.9%)	0.536
Killip class >1	437/462 (94.6%)	399/428 (93.2%)	422/447 (94.4%)	423/448 (94.4%)	0.815
TIMI risk score	2.17±1.94	2.47±2.09	2.45±2.10	2.59±2.02	0.008
(mean±SD, median (IQR))	2.0 (1.0–3.0) (n=459)	2.0 (1.0–4.0) (n=428)	2.0 (1.0–4.0) (n=446)	2.0 (1.0–4.0) (n=439)	
Field triage	397/462 (85.9%)	317/429 (73.9%)	287/448 (64.1%)	198/449 (44.1%)	<0.001
GPIIBIIIA blocker*	131/393 (33.3%)	120/385 (31.2%)	131/383 (34.2%)	118/381 (31.0%)	0.718
ST-segment deviation	9.01±6.21	8.50±6.48	7.72±6.25	6.34±5.63	<0.001
(diagnostic ECG)	8.0 (5.0–11.0) (n=297)	7.0 (4.0–11.0) (n=279)	6.0 (4.0–10.0) (n=311)	5.0 (3.0–9.0) (n=303)	
Multivessel disease	247/462 (53.5%)	213/429 (49.7%)	234/447 (52.3%)	249/447 (55.7%)	0.342

*Administered in the acute phase.

BI, balloon inflation; CABG, coronary artery bypass graft; DM, diabetes mellitus; GPIIBIIIA, glycoprotein IIBIIIA; MI, myocardial infarction; min, minutes; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
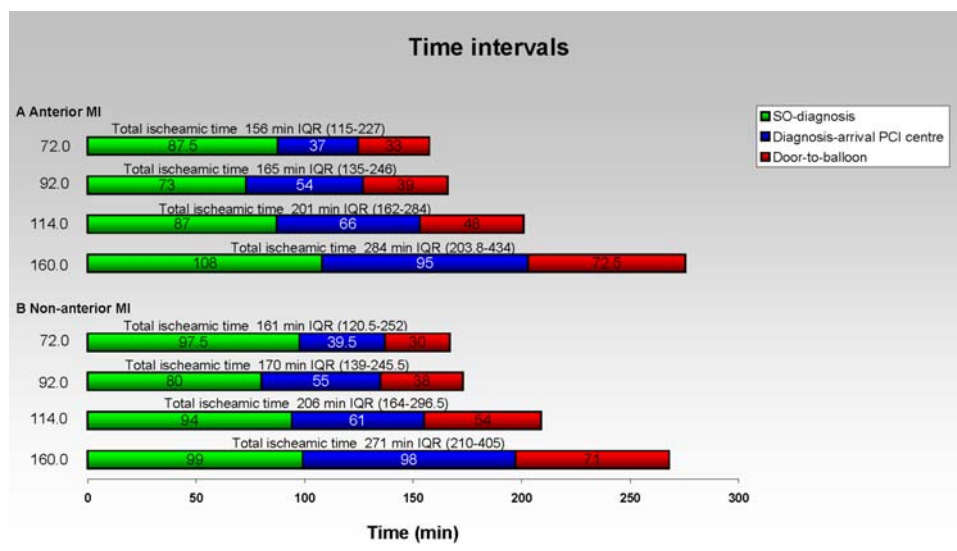
Figure 1 Time delays. The different time intervals are shown for patients with an anterior MI (A) and patients with a non-anterior MI (B). MI, myocardial infarction; min, minutes; PCI, percutaneous coronary intervention; SO, symptom onset.

Non-anterior MI

The baseline characteristics are described in table 1. Patients with prolonged system delay more often had a previous CABG, were less often diagnosed in the field and had less ST-deviation on the diagnostic ECG. There was a difference in previous MI and TIMI risk score among the quartiles of system delay. The culprit vessel in 1231 patients (68.8%) was the right coronary artery and in 425 patients (23.8%) it was the circumflex artery. The time intervals are illustrated in figure 1B. All time delays were significantly different between the quartiles of system delay. The median follow-up time was 5.2 (3.6–6.8) years. System delay was not associated with a large enzymatic infarct size (table 2). After Cox regression analysis, system delay was not associated with 30-day or with long-term mortality (figure 2B).

DISCUSSION

The present study is the first that assesses the effect of system delay on 30-day and on long-term mortality in patients with anterior and non-anterior MI separately. Interestingly, our results demonstrate that in patients with an anterior MI, system delay was significantly associated with 30-day and with long-term mortality. This effect was not apparent in patients with a non-anterior MI.

As demonstrated by Terkelsen et al,[4] system delay seems to be the reasonable time delay to focus on in non-randomised studies, since confounding, selection bias, information bias and recall bias hamper the other currently discussed time delays. Another advantage of this time delay is that this delay can be optimised during the prehospital triage as well as during the inhospital triage.

Highly trained paramedics from several ambulance services transfer their patients to our high volume Isala

Hospital where over 2000 PCIs are performed yearly. Even though all prehospital and inhospital strategies and procedures are optimised, the variation between the quartiles of system delay differed between 72 min (Q1) vs ≥160 min (Q4). A possible explanation for the variations in system delay is the fact that very sick patients are also included in this study and these patients have longer delays. As demonstrated, in general, the TIMI risk score increases with system delay in both patient groups. Furthermore, D2B time increased with system delay despite an increase in patient delay (time from SO diagnosis). The latter might be explained by the fact that in patients with the longest system delay (Q4), a decrease in symptoms was more often demonstrated after arrival in the PCI hospital. Non-system reasons might also account for these findings. Examples of non-system delays include delays in providing procedure consent, difficult access, difficulty in crossing the culprit lesion and patients who have a cardiac arrest requiring intubation before PCI.[11]

An increase in 30-day and long-term mortality was demonstrated with system delay in patients with an anterior MI. We anticipated that in these patients also an increase in infarct size would be demonstrated since a large amount of myocardium is at risk in these patients; thus, anterior MI is a strong baseline determinant of infarct size.[12] Furthermore, the association between system delay and infarct size has recently been demonstrated by Lønborg et al[13] and Tödt et al.[14] In our population, however, only an increase in infarct size was demonstrated in patients with an anterior MI in the first three quartiles of system delay (Q1–Q3). An explanation for this result might be that patients with the longest system delays (Q4) had less severe and distinct symptoms, and less deviations on the ECG, which has consequently lead to a prolonged D2B time. In addition,
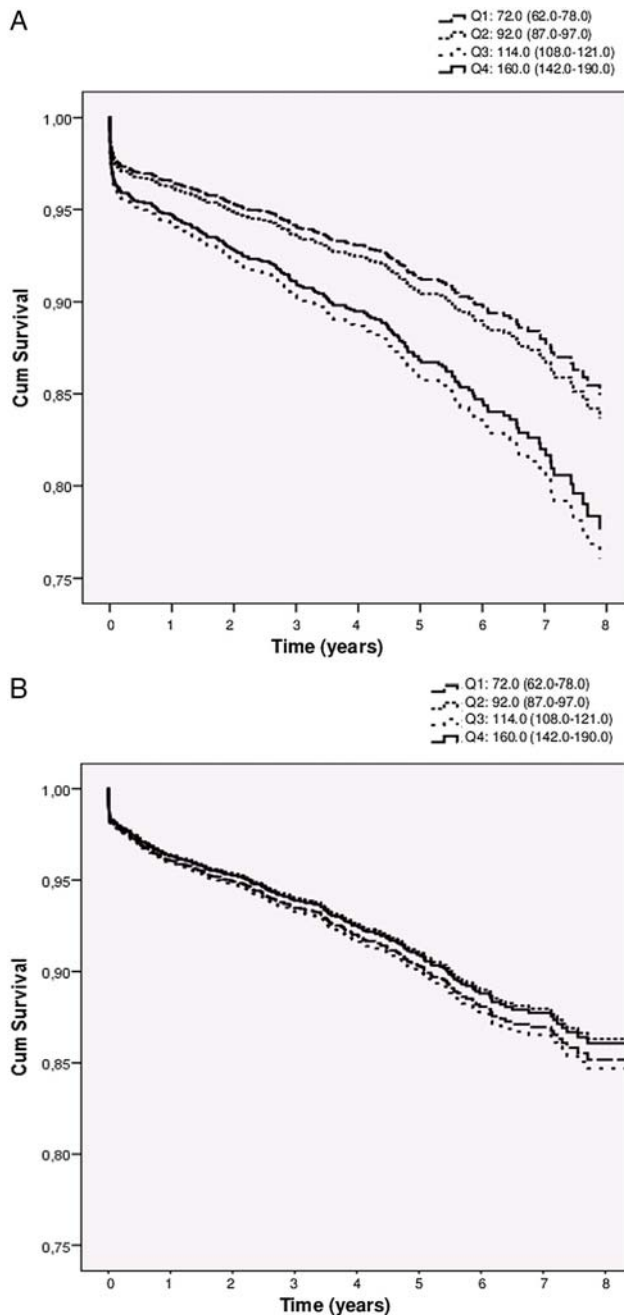
Figure 2 Mortality. Cox regression curves are shown for long-term mortality for patients with an anterior myocardial infarction (MI), (A) and patients with a non-anterior MI (B).

Lønborg et al and Tödt et al used MRI to assess the myocardial area at risk; this was not used in our study.

While prolonged system delay is associated with an increased mortality, especially in patients with an anterior MI, it is of the greatest importance to minimise system delay as much as possible. Therefore, currently several strategies have been developed to reduce system delay and other time delays. First, it is very important that the patients are triaged in the field by an ambulance and are transferred straight to the catheterisation laboratory of the PCI centre, bypassing the non-PCI

Table 2 Procedural characteristics, infarct size and mortality

System delay in quartiles (min)	Q1: 72.0 (62.0–78.0)	Q2: 92.0 (87.0–97.0)	Q3: 114.0 (108.0–121.0)	Q4: 160.0 (142.0–190.0)	p for trend
Characteristic					
Anterior MI					
	(n=313)	(n=321)	(n=323)	(n=296)	
TIMI flow 2/3 pre-PCI	111/312 (35.6%)	110/321 (34.3%)	127/323 (39.3%)	109/295 (36.9%)	0.443
TIMI flow 2/3 post-PCI	307/312 (98.4%)	316/321 (98.4%)	314/323 (97.5%)	288/295 (97.6%)	0.361
Infarct size >75th percentile	107/306 (35.0%)	122/313 (39.0%)	130/317 (41.0%)	91/288 (31.6%)	0.562
30-day mortality	8/313 (2.6%)	10/321 (3.1%)	22/323 (6.8%)	22/296 (7.4%)	0.001
Long-term mortality	40/313 (12.8%)	44/321 (13.7%)	78/323 (24.1%)	67/296 (22.6%)	<0.001
Non-anterior MI					
	(n=462)	(n=429)	(n=448)	(n=449)	
TIMI flow 2/3 pre-PCI	130/459 (28.3%)	148/424 (34.9%)	156/447 (34.9%)	146/447 (32.7%)	0.176
TIMI flow 2/3 post-PCI	451/459 (98.3%)	410/424 (96.5%)	435/447 (97.3%)	430/447 (96.2%)	0.127
Infarct size >75th percentile	78/451 (17.3%)	65/420 (15.5%)	70/438 (16.0%)	82/441 (18.6%)	0.590
30-day mortality	11/462 (2.4%)	13/429 (3.0%)	13/448 (2.9%)	13/449 (2.9%)	0.676
Long-term mortality	61/462 (13.2%)	64/429 (14.9%)	69/448 (15.4%)	73/449 (16.3%)	0.195

MI, myocardial infarction; min, minutes; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

centres and the emergency department of the PCI centre.[15] In our population, the benefit of this implemented strategy was obvious, that is, it was demonstrated that the amount of patients triaged in the field by an ambulance in Q1 was almost twice compared with the amount in Q4. Second, detailed identification of the time delays is essential so that an understanding can be gained. Third, collaborative discussions and feedback to staff involved in the care of patients with STEMI can make sure that the time delays can be optimised as much as possible. Points of discussion and feedback at present are (1) ECG recording by the highly trained paramedics in the ambulance, (2) central judgement of an ECG in the hospital, (3) timely preparation of catheterisation laboratory, and (4) prehospital and inhospital logistics.[16]

Limitations

First, the time of diagnosis was used together with the time of reperfusion therapy as a proxy for system delay. Information on the time of FMC was not available for all patients. However, a random sample of 94 cases revealed that in 83% of these patients, the difference between FMC (ie, EMS call) and diagnosis was ≤10 min. Second, since the project was not randomised and dispersed over several years, the risk of unknown confounders exists. Third, the level of peak CK within 24 h was used as surrogate parameter for infarct size.

CONCLUSIONS

Prolonged system delay significantly increased short-term as well as long-term mortality in patients with an anterior MI. This effect was not demonstrated in patients with a non-anterior MI. Therefore, it is of the greatest importance to minimise system delay in patients who present with an anterior MI.

Author affiliations
[1]Diagram B.V., CRO, Zwolle, The Netherlands
[2]Department of Cardiology, Isala Hospital, Zwolle, The Netherlands
[3]Department of Cardiology, St Antonius Hospital, Nieuwegein, The Netherlands
[4]Department of Cardiology, Radboudumc, Nijmegen, The Netherlands

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